UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2014-1547

THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK,

Appellant,

v.

ILLUMINA, INC.,

Appellee.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2012-00006.

APPELLEE'S BRIEF

NON-CONFIDENTIAL

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CASES

FEDERAL STATUTES

TABLE OF ABBREVIATIONS AND CONVENTIONS

A*x*(:*y*)	Page *x* of the Joint Appendix (at line *y*)
Illumina	Illumina, Inc.
Columbia	The Trustees Of Columbia University In The City Of New York
The Board	United States Patent and Trademark Office, Patent Trial and Appeal Board
IBS	Intelligent Bio-Systems, Inc.
SBS	Sequencing by synthesis
'869 patent	U.S. Patent No. 7,790,869
'698 patent	U.S. Patent No. 7,713,698
'575 patent	U.S. Patent No. 8,088,575
Anazawa	PCT Publication No. 98/33939
Dower	U.S. Patent No. 5,547,839
Seela	U.S. Patent No. 4,804,748
Solexa	Patent App. No. 0129012.1
Stemple	U.S. Patent No. 7,270,951
Rabani	PCT Publication No. WO 96/27025
Tsien	PCT Publication No. WO 91/06678
Prober	James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336-341 (1987)
IPR	*inter partes* review

CERTIFICATE OF INTEREST

Trustees of Columbia Univ. v. Illumina, Inc.

2014-1547

Counsel for Petitioner-Appellee certify the following:

1. **The full name of every party or amicus represented by me is:**

Illumina, Inc.

2. **The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:**

N/A.

3. **All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:**

No parent corporation or publicly held corporation owns 10% or more of Illumina, Inc.'s stock.

4. **The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or are expected to appear in this court are:**

Weil, Gotshal & Manges LLP – Edward R. Reines, Derek C. Walter, Marion M. Read, Audrey L. Maness, Michele A. Gauger

Reinhart Boerner Van Deuren s.c. – Robert Lawler, James Morrow

Foley & Lardner – Jeffrey N. Costakos

STATEMENT OF RELATED CASES

Illumina incorporates by reference Columbia's Statement of Related Cases.

The three appeals before the Court proceed from IPRs of similar patents. The Court ordered that these appeals be treated as companion cases. Dkt. No. 13. To facilitate the Court's review, Illumina designates its '698 patent brief in this appeal as the lead brief. This brief includes arguments substantially similar to those found in the '575 patent brief (Appeal No. 2014-1548) and the '869 patent brief (Appeal No. 2014-1550). Sections that largely overlap across the three briefs are: (1) the Preliminary Statement, (2) the Statement of the Case, (3) the section regarding obviousness, (4) the section regarding secondary considerations, and (5) the section providing Illumina's response to Columbia's complaints regarding the Board's procedural framework. The '575 patent brief and '869 patent brief include additional material targeted to specific prior art the Board relied upon for those patents along with argument directed to Columbia's motions to amend.

PRELIMINARY STATEMENT

In shotgun style, Columbia's appeal presents myriad substantive and procedural issues. All three companion appeals, however, boil down to one key question: would it have been obvious to use a deazapurine as an alternative to a regular purine in nucleotides when that technique had long been disclosed in the

art? Because the answer must be yes given the state of art, the Board had ample basis to conclude that all of Columbia's claims are invalid.

The proceedings before the Board reveal why this is the central question on appeal. In its three IPR requests, Illumina raised many independent invalidity grounds, including 12 grounds of anticipation based on Tsien, Dower, and Stemple. Recognizing the strength of Illumina's anticipation evidence, Columbia used its preliminary response solely to try to persuade the Board not to institute IPR based on ***anticipation***. Columbia was largely unsuccessful—except with regard to the '698 patent, which includes a deazapurine in all claims. For this one patent, the Board declined to institute an IPR based on anticipation because Tsien and Stemple supposedly do not themselves disclose the use of deazapurine in their nucleotides.

In contrast to the'698 patent, the majority of claims in Columbia's '575 and '869 patents do ***not*** require a deazapurine. Deazapurine is included in only a few dependent claims. Thus, for these two patents, the Board instituted IPR based on anticipation by Tsien, Stemple, and/or Dower.

Columbia's response to the PTAB's decisions to institute IPRs is critical to understanding the scope of this appeal. Instead of fighting the Board's determination that Tsien, Stemple, and Dower anticipate claims that have no deazapurine, Columbia ***canceled*** all those claims—without reservation. Columbia

moved to amend, proposing substitute claims ***identical*** to the original claims except with the added requirement of a deazapurine. Columbia failed to defend any claim without a deazapurine requirement.

By falling back to this "deazapurine" battle-line, Columbia tacitly conceded that Tsien, Stemple, and Dower disclose all limitations of these claims except deazapurine. As documented in this brief, the evidence supporting this conclusion is overwhelming and thus forced Columbia's "deazapurine" retreat. Columbia's heavy bet on its "deazapurine" position is nevertheless a loser. Deazapurines were part of the DNA sequencing art since the late 1980s and had become ubiquitous in the 1990s due to numerous well-known benefits of deazapurines for sequencing well before Columbia filed for its patents. Illumina's primary reference, Tsien, specifically recommends synthesizing nucleotides based on the procedures disclosed in Prober, which expressly includes the use of deaza-type purines. Likewise, Stemple expressly references using deazapurines as described in Anazawa.

Further, although Columbia presents lengthy arguments on secondary considerations of nonobviousness, it never contends that using a deazapurine is connected to those considerations. Columbia instead relies on ***other*** features that are undeniably present in Tsien, Stemple, and Dower.

Ultimately, Columbia's actions speak louder than its words. Columbia's retreat to claims requiring deazapurine belies its insistence that the prior art does not teach the combination of 3'-OH caps plus cleavable base labeling. In this light, Columbia's case is revealed as nothing more than an attempt to salvage claims invalid due to anticipation by adding a deazapurine, even though that was a standard technique commonplace in the prior art. The law of obviousness, however, prohibits this maneuver.

Columbia attempts to bolster its appeal by complaining that the Board supposedly committed procedural errors. It alleges that the Board failed to make necessary findings, improperly allocated burdens, and failed to honor the adjudicative nature of IPR. But Columbia never identifies these alleged errors with particularity, let alone explains how they could constitute reversible error. The Board was thorough and thoughtful in adjudicating this dispute. It asked over 100 questions at oral argument and issued a 46-page written opinion in which it walked through all of Columbia's expert witness evidence and thoroughly reviewed Columbia's secondary considerations.

The Board's analysis is correct and supported by substantial evidence. The decision should be affirmed.

ISSUE PRESENTED

Whether substantial evidence supports the Board's determination that claims 1-7, 11-12, 14-15, and 17 of the '698 patent are obvious.

STATEMENT OF THE CASE

I. The State Of The Art Of DNA Sequencing By Synthesis

The trio of patents at issue in the companion cases relate to a method of DNA sequencing called sequencing by synthesis ("SBS"). SBS is a sequencing method where nucleotides are incorporated one-by-one to synthesize a DNA chain. As nucleotides are sequentially incorporated, they are "read" to determine the sequence. A3280:5-11.

Columbia's introduction to DNA sequencing attempts to paint a picture of one man's supposed flash of genius. However, researchers began developing non-Sanger based methods of DNA sequencing in the late 1980s. A3729:18-22; A132(2:7-11). By the late 1990s, the prior art documented numerous solutions to the issues underlying a practical SBS method—including the very solutions Columbia now attempts to claim as Dr. Ju's alleged breakthrough. A3173-74.

A. A Labeled Base And 3'-OH Cap Were Preferred By The Late 1990s

Dr. Ju did not invent the concept of attaching a label to a nucleotide base for sequencing. Well before Columbia's October 2000 filing date, many prior art references documented the use of nucleotides for DNA sequencing with ***both*** a

removable 3'-OH cap and a detectable label attached ***to the base***. Exemplary references include Tsien, Dower, and Stemple.

Tsien teaches an SBS method where a template DNA strand coupled to a solid support is sequenced by sequentially adding fluorescently labelled nucleotides with 3'-OH blocked ends. A3011:17-3019:33. Tsien discloses labelling the ***base*** of the nucleotide: "there are a number of alternatives–particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a remote position ***such as the base***." A3028:35-3029:2.[1] Making clear that Tsien teaches base-labeling, he states that such a "method involves the use of a fluorescent tag attached ***to the base*** moiety." A3029:5-6.

Likewise, Dower teaches using chain-terminating nucleotides having ***both*** a removable fluorescent label attached ***to the base*** and a removable blocking group located at the 3'-OH of the deoxyribose. A3086(14:50-53), A3087(15:33-40, 15:52-56), A3088-89(18:64-19:10); A3077 Fig. 9. Similarly, Stemple describes a nucleotide "configuration" in which a photolabile group is attached to the 3'-OH and a "fluorochrome-photolabile linker conjugate is attached directly ***to the base***." A5020(22:53-57).

[1] Emphasis supplied unless otherwise noted.

Dr. Ju's patent acknowledges that those in the art had understood since at least 1994 that base-labeled nucleotides could be recognized by DNA polymerases:

> On the other hand, it is known that modified DNA polymerases (Thermo Sequenase and Taq FS polymerase) are able to recognize nucleotides with extensive modifications with bulky groups such as energy transfer dyes at the 5-position of the pyrimidines (T and C) and at the 7-position of purines (G and A) (Rosenblum et al. 1997, Zhu et al. 1994).

A132(2:43-49); *see also* A133(3:11-15) (citing literature from 1978 and 1994 as confirmation that polymerase will incorporate nucleotides so long as the 3'-OH cap is not too large).

By 1999 base-labeled nucleotides were favored over a fading alternative, 3'-OH-labeled nucleotides, because it had become clear that bulky labels attached at the 3'-OH did not fit well within the active site of the DNA polymerases required for SBS. For instance, Stemple teaches that a base-labeled configuration "may be preferred if it is found that steric hindrance of large fluorochrome groups attached to the 3'-OH of the nucleotide prevent the nucleotide from entering the polymerase." A5020(22:64-67). This was confirmed by Welch and colleagues at Texas A&M, and all Dr. Ju's patents cite Welch for the drawbacks of 3'-OH nucleotides (as compared to base-labeled nucleotides):

> More recent work in the literature exploring DNA sequencing by a synthesis method is mostly focused on designing and synthesizing a photocleavable chemical moiety that is linked to a fluorescent dye to cap the 3′-OH group of deoxynucleoside triphosphates (dNTPs)

> (***Welch et al. 1999***). ***Limited success for the incorporation of the 3'-modified nucleotide by DNA polymerase is reported.*** The reason is that the 3′-position on the deoxyribose is very close to the amino acid residues in the active site of the polymerase, and the polymerase is therefore sensitive to modification in this area of the deoxyribose ring.

A132(2:33-43); *see also* A5400:1-7, 15-21 (testimony of Illumina's expert, Dr. Kevin Burgess, regarding his publication with Welch); A5688:24-A5690:21 (same).

As correctly found by the Board and supported by substantial evidence, Dr. Ju was ***not*** the first to conceive of base-labeled nucleotides. Nor was he the first to have the "spatial insight," Columbia.Br.10, that would lead one of skill in the art to use base-labeled nucleotides instead of 3'-OH labeled nucleotides.[2]

B. Using Deazapurine Nucleotides Labeled At The 7 Position Was Preferred

Dr. Ju was also not the first to conceive of using C-7 substituted deazapurines (*i.e.*, purine bases with the nitrogen atom at the 7-position replaced by a carbon atom with a linker/label attached) for DNA sequencing. As far back as 1987 this was established in Prober's article, *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides.* Prober disclosed

[2] Although not relied upon by the Board, Welch's February 1999 publication negates any contention that Dr. Ju was the first to have the "spatial insight" regarding sensitivity of DNA polymerase to bulky modifications at the 3'-OH. *See* A5722 (noting that 3-OH labeled fluorescent nucleotides "tend to be too big to fit into the active site of DNA polymerase").

nucleotides for DNA sequencing where the label was attached to the C7-position of the deazapurine. A3064 Fig. 2. Just two years later, Seela broadly taught that deazapurine nucleotides are useful in sequencing approaches that use a DNA polymerase—which SBS does. *See* A3157(4:4-10) ("7-deaza-2'-deoxyguanosine triphosphate can be used instead of 2'-deoxyguanosine triphosphate in those sequencing methods for DNA in which the use of DNA polymerase is necessary.").

By 1999, C7-labeled deazapurines had become commonplace for DNA sequencing reactions with labeled nucleotides. *See, e.g.*, A4250:16-4251:6[Trainor Dep. Tr.] ("**Q.** The use of ddNTP that were–that had fluorescent labels attached to the 7-deazapurine position, that was common by the year 2000? **A.** For Sanger sequencing, yes.); A4380:7-4381:9. The ubiquity of deazapurines was ***not*** limited to Sanger sequencing. Indeed, numerous workers in the follow-on field of SBS used 7-substituted deazapurines. A3177-3178[Weinstock Decl.] ¶ 59; A3452:15-3453:22, A3590:6-93:25, A3594:21-24, A3598:3-8, A3652:10-14[Weinstock Dep. Tr.]. Notably, in his own SBS patents, Dr. Ju acknowledges this by citing the 1987 Prober reference for the proposition that deazabase-labeled nucleotides were the product of "well-established procedures." A143(24:64-67).

This widely accepted use of 7-deazapurines in sequencing stemmed from multiple motivations recognized in the prior art. It had long been known that

attaching a label to the C7-labeled deazapurine minimizes interference with the incorporation of nucleotides into a DNA strand by a polymerase.[3] For instance, in 1987, Hobbs explained that "positioning the linker on the 5-position of pyrimidine nucleotides ***and the 7-position of 7-deazapurine nucleotides*** eventually places the linker and reporter in the major groove when the nucleotide is incorporated into double-stranded DNA (this will serve to minimize interference with hybridization and other processes, which require that a double-stranded conformation be possible)." A5102(27:44-59); *see also* A3175-3176, A3199[Weinstock Declaration] ¶¶ 43-49, 98.

Other benefits of 7-deazapurines were known, including that they were more easily added to growing DNA strands and resulted in more stable DNA end products that better allowed subsequent incorporations. A5102(27:44-59)[Hobbs]; A3603:21-3604:1[Weinstock Dep. Tr.]; A4361:8-11, A4408:19-25[Trainor Dep. Tr.]. Additionally, it was known that deazaguanine–based nucleotides allow for more effective sequencing of DNA regions dense with "C" and "G" bases, which can present special problems, and that attachment at the 7 position (as opposed to the 8 position) of a deazapurine facilitated stable linker arm attachment. A3378:5-3379:2; A3393:4-3394:12, A3399:24-3403:4[Weinstock Dep. Tr.]; A3176 ¶ 49.

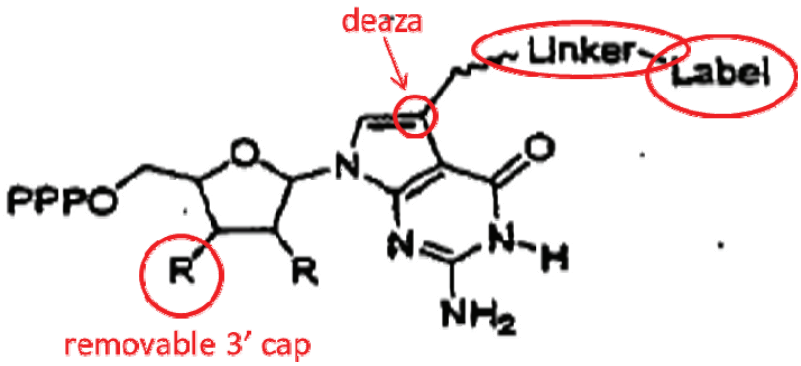
[3] It was not possible to link a label to this advantageous 7 position of a purine in a non-deazapurine due to stability issues. A3176[Weinstock Decl.] ¶¶ 49-50, 52.

II. Independent Development Of Dr. Ju's Alleged Invention

Given the knowledge described above, multiple researchers independently arrived at the alleged inventions claimed in Columbia's patents, either simultaneously or before Dr. Ju.

Barnes and coworkers at Solexa (later acquired by Illumina) conceived of an SBS approach where "the incorporation of the labelled nucleotide is carried out by the polymerase enzyme, and the incorporation event determined." A3756:17-18[Solexa Patent App.]. Solexa conceived of its SBS approach no later than December 2001, long before Dr. Ju's patent applications published. Notably, Solexa—like Dr. Ju—referenced Welch's 1999 work showing that 3-'OH labeled nucleotides were too bulky to be incorporated by polymerase. A3750:5-10.

In Solexa's approach, "there is no detectable label attached at the ribose 3' position. This ensures that steric hindrance with the polymerase enzyme is reduced, while still allowing control of incorporation using the protecting group." A3755:21-24. Given the established difficulties associated with bulky labels at the 3'-OH, Solexa instead proposed nucleotides in which the label was attached ***to the base***. One specific type of base-labeled nucleotide Solexa proposed included C7-substituted deazapurines:

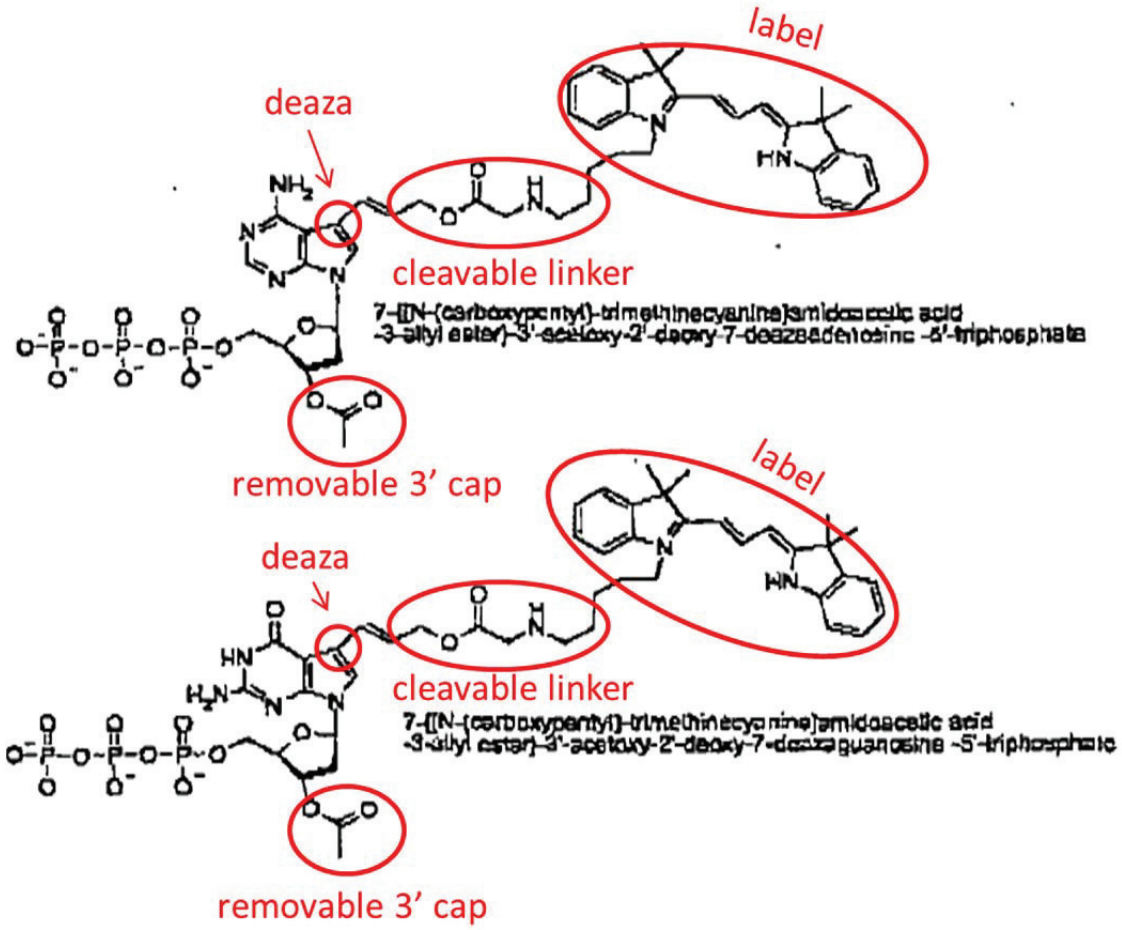


A3767 Fig. 1;[4] *see also* A3755:17-24 (describing a protecting group at the 3'-OH that can be "removed under defined conditions to allow polymerization to occur"). The nucleotide shown above discloses the allegedly novel combination claimed in Dr. Ju's patent, including an unlabeled 3'-OH cap, a label attached to the base, a cleavable linker between the label and the base, and a deazapurine. Columbia.Br.10. Columbia's expert confirmed this at trial. A4081:15-4101:16, A4431:21-4432:17, A4488:18-4494:10[Trainor Dep. Tr.].

Although not relied on by the Board, it is noteworthy that Solexa was not the only company to independently conceive of Dr. Ju's alleged inventions. No later than June 2000, before Dr. Ju's earliest filing date, Odedra and co-workers at Amersham conceived of nucleotides for SBS involving "the separation of blocking and reporter moieties on a nucleotide and the use of linkage groups cleavable by

[4] Red annotations are supplied throughout for convenience.

enzymatic action." [5] A5129:28-30[Amersham Patent App. No. 0013276.1]. Like Solexa, Amersham put the label on the base rather than the 3'-OH because "by attaching the bulky report moiety in the 3' position of the nucleotide, the ability of the DNA polymerase to recognize or tolerate the nucleotide is reduced." A5128:20-21. Nucleotides described by Amersham included the combination that Dr. Ju made later and asserts is inventive:



[5] The work of Odedra and colleagues is not prior art under § 102 solely because it was first disclosed in a United Kingdom filing.

A5145. Like the Solexa nucleotides, the Amersham nucleotides include Dr. Ju's allegedly novel combination. A5127, A5129-30, A5133; A4502:17-4515:14[Trainor Dep. Tr.]. Thus, the undisputed record shows that Dr. Ju was not the first to conceive of his alleged invention and that others had simultaneously and independently conceived of the same combination of known techniques.

III. The Trial

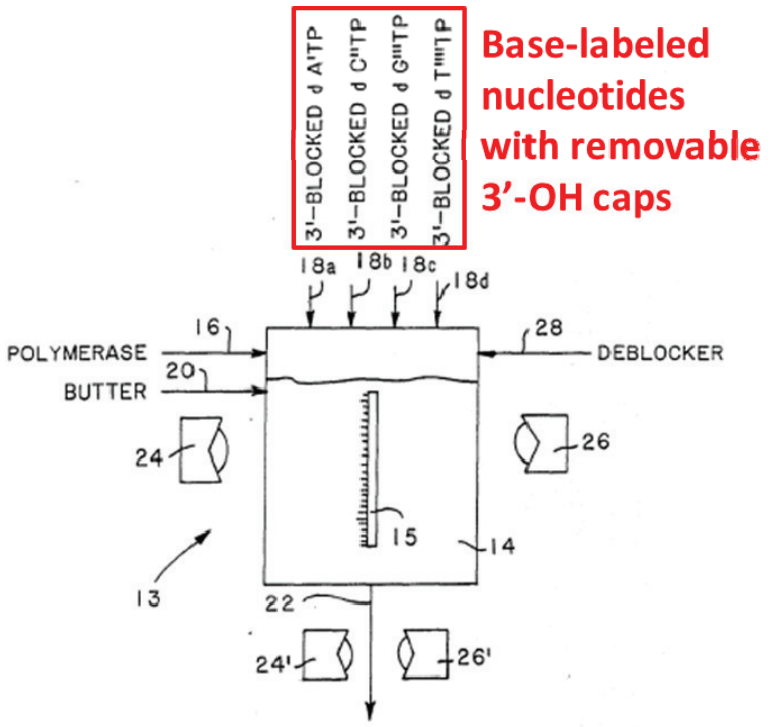
A. Illumina's Case

Illumina's obviousness case was rooted in the state of the art summarized above. Illumina relied primarily upon the combination of Tsien with either Prober or Seela to establish that claims 1-7, 11, 12, 14, 15, and 17 are obvious. For claim 12, which adds the requirement of a "microarray," Illumina further relied upon the Rabani reference. Illumina's positions were supported by the testimony of Dr. George Weinstock, who has over 15 years of experience managing large-scale DNA sequencing projects. A3162-3163[Weinstock Decl.] ¶¶ 8-9.

Columbia relied almost exclusively on the testimony of Dr. George Trainor. Dr. Trainor has no experience with large scale DNA sequencing nor did he talk to those who did. *See* A4494:24-25 ("I didn't go into sequencing labs and I don't go into biology labs."). In fact he has had "[n]o actual hands-on work on sequencing" since 1994—six years before the October 2000 priority date of the '698 patent. A4067:9-11.

1. The Combination Of Tsien With Prober Or Seela

The primary reference relied upon by the Board was Tsien. Tsien teaches an SBS method in which a template DNA strand is attached to a solid support and 3'-OH-blocked nucleotides are sequentially added to the template and detected to sequence the template. A3008:3-14, A3011:7-10, A3013:27-29. As Dr. Trainor confirmed, Figure 2 of Tsien depicts the nucleotides using apostrophes (*i.e.*, "dA′TP," "dC″TP," "dG‴TP," and "dT⁗TP") to indicate that that the label may be included on the base:

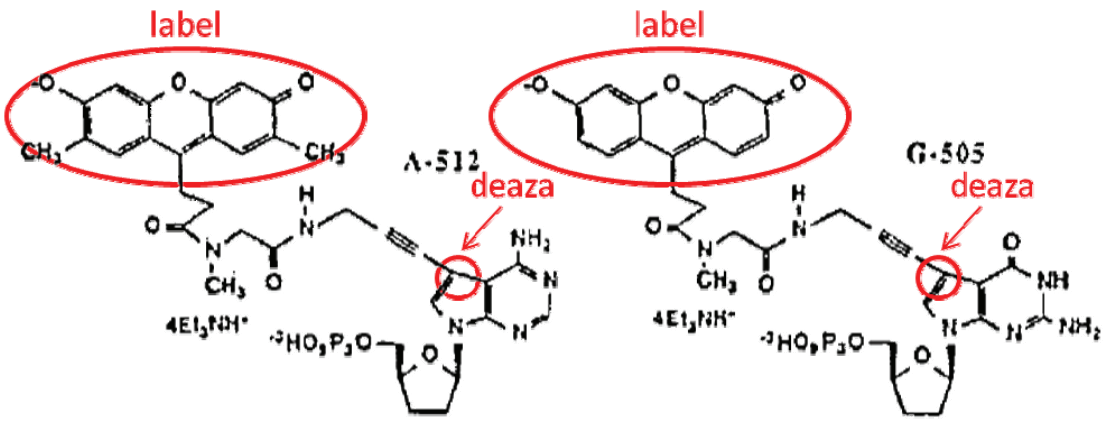


A3053; A3011:10-14; A4289:7-10. The text of Tsien further confirms that the label can be on the base: "there are a number of alternatives–particularly the formation of a 3'-blocked dNTP analogue containing a label ***such as a fluorescent***

group coupled to a remote position such as the base." A3028:35-3029:2. Tsien specifically explains that "[o]ne method involves the use of a fluorescent tag attached ***to the base*** moiety." A3029:5-6. Tsien explains that such "base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence," thus demonstrating that those in the art understood they would be recognized and incorporated by a DNA polymerase, as required for SBS. A3029:5-12.

Tsien further teaches that the labels for each of the four nucleotides may be "different" and that they may be attached by a "cleavable tether" to "permit removing the fluorescent group before the next successive nucleotide is added." A3012:7-9, 3029:19-29; *see also* A4299:2-16 (Dr. Trainor confirms that Tsien discloses a cleavable tether). Finally, Tsien designates a removable cap on the 3'-OH group of the sugar because "the sequencing scheme ***requires*** the blocking group to be removed to yield a viable 3'-OH site for continued chain synthesis." A3024:29-31. Tsien thus expressly discloses all elements of the asserted claims, except arguably using a deazapurine.

But Tsien is not silent on using deazapurines. Tsien recommends using the nucleotides described in the well-known 1987 Prober reference. Prober discloses ***only*** 7-substituted deaza-type purines:



A3064 Fig. 2; *see also* A3063 col. 1("The linker is attached to the 5 position in the pyrimidines ***and to the 7 position in the 7-deazapurines***."). Columbia's expert confirmed that in Prober the preferred place to attach the label in the purines—in fact the only place disclosed—is the 7-deaza position. A4334:10-14[Trainor Dep. Tr.] ("**Q.** So in your reference … the preferred place to attach the label in the purines was at the 7-deaza position, right? **A.** Yeah."); A4335:10-18.

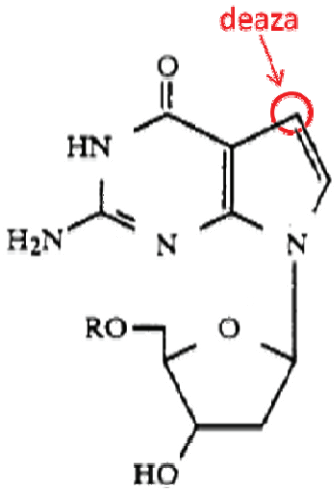
As Tsien explains, Prober showed incorporation of his 7-substituted deazapurines with fluorescent labels by Tsien's preferred polymerase, Sequenase™:

> One method involves the use of a fluorescent tag attached to the base moiety….This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence…***Prober et al. (1987) show enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™***.

A3029:5-18. Tsien teaches that the synthesis scheme for ddNTPs used in Prober should be used to produce fluorescent dNTPs for SBS: "One quite versatile scheme

is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags." A3030:13-14. Tsien therefore expressly endorses Prober's use of C7-labeled deazapurines as an effective way to couple a fluorescent label to a nucleotide base for DNA sequencing. A3181.

Seela, like Prober, is directed to nucleotides for DNA sequencing methods and also discloses using deazapurines, stating the "present invention provides 7-deaza-2'-deoxyguanosine nucleotides…[and] is also concerned with the use thereof in the sequencing of DNA." A3155(Abstract). An exemplary deazapurine from Seela is depicted below:



A3156(2:35-45). As noted above, Seela teaches using deazapurine nucleotides "in those sequencing methods for DNA in which the use of DNA polymerase is necessary." A3157(4:6-7). This, of course, includes SBS.

2. Rabani

Rabani relates to massive molecular parallelism applicable to DNA sequencing, which "may be applied to genome-scale sequencing methods." A3101:36-37. Rabani discloses detection of "multiple probes (*i.e.* in arrays with parallel detection provided)." A3107:12-13.

Although Columbia asserts that "Rabani does not, however, describe a microarray of nucleic acids," Columbia.Br.23, its expert testified otherwise. Dr. Trainor acknowledged that Rabani discloses an array of different polynucleotide molecules at a density conducive to detection. A4453:8-11 ("**Q.** So Rabani discloses an array of different polynucleotide molecules? **A.** It does."); A4453:12-14 ("**Q.** At a density that is convenient for detection? **A.** Apparently.). He then conceded that Rabani discloses a microarray. A4453:20-22 ("[T]hat would be a microarray of templates, yeah. I would think so.").

B. Columbia's Secondary Consideration Contentions

Columbia contended before the Board that secondary considerations of non-obviousness supported its position. Columbia's arguments were primarily based on Dr. Trainor's testimony. Although Columbia asserted six secondary considerations before the Board, on appeal it raises only four: (1) unexpected properties, (2) commercial success, (3) copying, and (4) licensing.

For every claim in all three patents in the companion cases, Columbia presented the exact same evidence and argument. Columbia did not tie any specific features of any single claim to any secondary consideration, nor did it differentiate among claims or even patents. Critically, Dr. Trainor never asserted that the deazapurine "feature" of the asserted claims was connected to even a single secondary consideration.

To establish a nexus, Columbia and Dr. Trainor relied solely on a single feature allegedly present in all claims of its three patents: the separation of the label from the removable 3'-OH cap by attaching the label to the base via a cleavable linker. That is, to establish a nexus, Dr. Trainor relied solely on a concept that he acknowledged was already in the prior art, including in Tsien. *See* A3794 ¶ 28 (Dr. Trainor opines that "Tsien also mentions as an alternative, nucleotide analogues which include a label attached to the base (Exhibit 1002, page 28, ll. 5-6) and the possibility of the label being attached to the nucleotide analogue by means of a cleavable tether (Exhibit 1002, page 28, ll. 19-21)").

IV. The Board's Final Written Decision

The Board's Final Written Decision was based on the evidentiary record as probed during extensive oral argument. The three-member panel asked over one hundred questions. The Board's 46-page written decision held all the original

claims unpatentable, and reflected the same depth of engagement that had been on display at oral argument. A46.

The Board's final written decision included findings on the obviousness factors set forth in *Graham et al. v. John Deere Co. of Kansas City*, 383 US 1, 17-18 (1966). First, the Board noted Columbia's inaccurate characterization of the scope and content of the art:

> Columbia's characterization of the prior art as having "some interest in base-labeled nucleotide analogues" understates the interest level shown in the prior art. Tsien and Dower, cited in this *inter partes* review, and Stemple III, cited in related proceedings, describe SBS methods, which disclose base-labeled nucleotides and nucleotides containing a removable chemical moiety at the 3'-OH position….

A5-6. The Board then further documented the narrow differences between the prior art and the claimed invention, summarizing Dr. Trainor's opinion that one would need to make seven different changes to the nucleotides disclosed in the prior art to achieve the claimed invention. A16-17. It analyzed every alleged difference. It conducted a close review of Dr. Trainor's arguments and evidence and explained why Dr. Trainor was wrong on every point. It identified Dr. Trainor's numerous concessions about the prior art and cited dozens of disclosures in the prior art establishing the narrow difference between the claimed inventions and the prior art. A16-27.

Turning to Columbia's secondary considerations, the Board emphasized that "the deazapurine is not said by Columbia to be responsible for the unexpected result" and cited to Dr. Trainor's testimony. A32. Dr. Trainor attributed the success of Ju's invention to the labeled base and 3'-OH removable cap, which the Board properly recognized was disclosed in Tsien. A33. It came to the same conclusion with regard to Columbia's evidence of attempted licensing, noting that the "invention recognized by Illumina as having merit is one which is described in Tsien with the removable 3'-OH capping group and base label." A38. Because Columbia's evidence of secondary considerations was connected solely to a feature taught in the prior art, the Board held that this evidence was insufficient to overcome Illumina's prima facie case of obviousness.

SUMMARY OF ARGUMENT

The substantial evidence supporting the Patent Office's obviousness determinations is straightforward:

- Tsien discloses all elements of the claims, except arguably using deazapurine as an alternative to a regular purine.
- As to using deazapurines, Tsien expressly teaches using the nucleotides described in Prober, which are C7-substituted deazapurines.
- Even absent this express encouragement, one of skill in the art would be motivated to combine the disclosure of Tsien with a deazapurine base due to the ubiquity and well-known benefits of deazapurines for sequencing.

- The near simultaneous and independent conception of Dr. Ju's alleged invention by multiple research groups shows that the prior art guides those of skill in the art to the claimed invention and confirms obviousness.

Dr. Trainor's contention that there was no motivation to combine and no expectation of success disintegrated on cross-examination. Dr. Trainor admitted that one skilled in the art could synthesize the claimed nucleotides using well-established procedures and would expect them to be useful for SBS. These key technical points are also acknowledged in the specification of Dr. Ju's patents.

Columbia's secondary consideration position does not negate the substantial evidence supporting the Board's ruling because none of it is connected to using deazapurine. Columbia indiscriminately presented the same evidence of secondary considerations for each of the 32 claims at issue across three patents in the companion cases, implicitly exposing the lack of a meaningful nexus to the claimed inventions. Further, Columbia's evidence of secondary considerations lacks nexus because the sole feature of all 32 claims upon which Columbia relies (attachment of a label to the base via a cleavable linker) was well-known in the prior art, including Tsien.

ARGUMENT

I. Standard Of Review

This Court reviews the Board's factual findings for substantial evidence and its legal conclusions de novo. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1251-52 (Fed. Cir. 2013) (citing *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000)). "A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding." *K/S Himpp v. Hear-Wear Technologies, LLC*, 751 F.3d 1362, 1364 (Fed. Cir. 2014) (citing *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)). This Court has noted that the "substantial evidence" standard of review for fact findings made by the Board makes the Appellant's burden on appeal "a challenging one." *Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1348 (Fed. Cir. 2013).

II. The Board Correctly Concluded That The Prior Art Establishes That The Asserted Claims Are Obvious

Columbia contends that the Board made "three unsupported inferential leaps" in its decision. Columbia.Br.35. Specifically, Columbia contends that the Board made unsupported "inferences" that those of skill in the art would have (1) made a nucleotide with a label attached to the base, (2) attached the label by a cleavable linker, and (3) used a deazapurine. *Id.*

Columbia ignores its decision to cancel all claims that do not include a deazapurine, a tacit concession that the prior art discloses the combination of all

claimed elements except arguably a deazapurine. It further ignores the overwhelming evidence establishing that using a deazapurine was not inventive, as confirmed by Columbia's inability to connect even one secondary consideration of nonobviousness to using a deazapurine. Ultimately, any doubt that the Board's analysis is correct is confirmed by the fact that multiple researchers simultaneously and independently arrived at the claimed invention either concurrently with or before Dr. Ju.

A. Tsien Discloses All Elements Of The Claims With The Arguable Exception Of A Deazapurine

Columbia states that "Tsien provided no motivation to try to use a nucleotide with a label on the base" and "did not teach a nucleotide with both a base-label and a cleavable linker." Columbia.Br.30. These denials are blind to the evidence.

Columbia's own expert testified on direct examination that Tsien discloses "nucleotide analogues which include a label attached to the base…and the possibility of the label being attached to the nucleotide analogue by means of a cleavable tether." A3794 ¶ 28 (citations omitted); *see also* A4299:2-7 (Trainor confirming this admission on cross-examination). This admission alone negates Columbia's argument to this Court that Tsien does not disclose a label attached to the base via a cleavable linker.

Columbia's expert could not avoid such an admission given the express teachings of Tsien. First, as to base-labeling, Tsien teaches that "there are a number of alternatives—particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a remote position ***such as the base***. This dNTP can be incorporated and the fluorescence measured and removed according to the methods described below." A3028:35-A3029:4. Likewise, Figure 2 of Tsien shows nucleotides containing a blocked 3'-OH group, with the notation that labeling is on the base, although it may occur elsewhere. A3053 Fig. 2; A3028:35-29:2. In a footnote, Columbia states that the "Board apparently misunderstood the figure as depicting the labels attached to the bases." Columbia.Br.38 n.7. The Board did not misunderstand anything. Tsien is clear that the notation in Figure 2 encompasses base-labeling: "[T]he fact that the indication of labeling appears associated with the 'nucleoside base part' of these abbreviations does not imply that this is the sole place where labeling can occur." A3011:10-15.

As to using a cleavable tether, Tsien is just as clear: "In another type of ***remote labeling*** the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. The ***tether can be cleavable*** if desired to release the fluorophore or other label on demand." A3029:19-23. Tsien further states that the label can be attached to "remote position ***such as the base***. This

dNTP can be incorporated and the fluorescence measured and removed according to the methods described below." A3028:35-A3029:4. The only removal method "below" is the cleavable linker discussed two paragraphs later. A3029:19-29; *see* A5583:21-A5584:22[Burgess Dep. Tr.].

Columbia nevertheless insists that the Board "acknowledged" that Tsien does not describe attaching a label to the base by the linker. Columbia.Br.41. Columbia misdescribes the Board's decision. The Board cited Tsien as giving "an express reason to use a cleavable linker when attaching a label to the deaza-substitued nucleotide: 'to release the fluorophore or other label on demand.'" A21. The paragraph of Tsien cited by the Board regarding "remote labeling" and the use of a "cleavable" tether is followed by exemplary structures that illustrate labels attached to the bases by tethers, thus confirming that the tether paragraph relied on by the Board (disclosing "cleavable" tethers) should be used in conjunction with a base-label. A3029-31.

On cross-examination, Columbia's expert confirmed that Tsien discloses attaching the label to the base via a cleavable linker. *See* A4170:4-8 ("**Q.** So Tsien discloses a dNTP analogue that is 3'-blocked and has a fluorescent label coupled to the base. **A.** Yes. In a general sense, yes, in a general notion of that."); A4289:7-10 ("**Q.** And they could be but are not necessarily attached to the base, agree? **A.** He's made that clear. Yeah."). A4299:2-7 ("**Q.** And then, he describes the ***labeling on***

the base through the use of a tether, beginning at line 19 on page 28, right? **A.** Line 19? Are you sure it's 19–yes, and another remote label, yes."); A4299:14-16 ("**Q.** And then he says 'the tether can be cleavable,' right? **A.** He does."). The Board decision is confirmed by the testimony of Illumina's experts, which is in accord with Dr. Trainor's admissions. A3448:13-A3449:19; A5585:15-22. Substantial evidence—both in the prior art and expert testimony—confirms that Tsien discloses all claimed features, except arguably a deazapurine.[6]

Columbia argues that the Board erred in finding that a skilled artisan would place the label on the base. Columbia.Br.37. Columbia asserts that a skilled artisan reviewing Tsien would have only placed the label on the 3'-OH because Tsien "prefers" that configuration and calls it "ideal." Columbia.Br.37. Yet, there is nothing in Tsien that disparages attachment to the base; rather, it describes base attachment as an "ideal" approach. *See* A3030:3-4 ("The C-8 position of the purine structure presents an ideal position for attachment of a label."). Tsien's section on label attachment, A3027-3031, spends three of five pages on the base

[6] Columbia's brief only contends that Tsien is deficient with regard to attachment of the label to the base via a cleavable linker and using a deazapurine. Columbia does not dispute that Tsien discloses other elements of the asserted claims, such as using a removable 3'-OH cap and using unique labels. Any such challenge would be without merit given the admissions of Columbia's expert regarding the disclosure of Tsien. A4176:2-7, A4285:16-19, A4288:12-21, A4288:25-89:6[Trainor Dep. Tr.].

labeled location, A3029-3031. Regardless, "a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). Likewise, a "reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.,* 567 F.3d 1314, 1327 (Fed.Cir. 2009).

By the late 1990s it was preferred in the prior art to place the label on the base. *See supra* at 5-8. For instance, Stemple taught that a base-labeled configuration "may be preferred if it is found that steric hindrance of large fluorochrome groups attached to the 3'-OH of the nucleotide prevent the nucleotide from entering the polymerase." A5020(22:64-67). Dr. Ju's patents (and Solexa's) cite the prior art work of Welch and colleagues as having confirmed the incompatibility of 3'-OH labeled nucleotides and DNA polymerases. A133(4:33-43); A5400:1-7, 15-21[Burges Dep. Tr.]; A3750. Consistent with this, Columbia's expert unambiguously agreed that Welch's work would have motivated one to try alternatives to 3'-OH labeling

Q. And the problems they identified here and the reason they are

> having difficulty [with 3'-OH labeling] was that the labels tend to be too big to fit in the active site of the DNA polymerases?
>
> **A.** Yes. So it's one of the things I might have done, had I been, you know, reading this and working with these folks the conclusion is let's try linking the dye differently. Right?

A4424:16-25. Tsien expressly teaches the base-labeled embodiment as an alternative because "a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence," A3029:10-12, one of Tsien's fundamental requirements, A3013:22-27. This is precisely the type of "[p]otent and promising activity in the prior art" that would have motivated one skilled in the art to choose the base labeled alternative. *Daiichi Sankyo Co. v. Matrix Labs.*, Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010).

Finally, Columbia raises non-specific allegations that the Board committed supposed structural and procedural errors in its analysis of whether the prior art disclosed attachment of a label to the base via a cleavable linker. Columbia's complaint that the board "shifted the burden of persuasion to Columbia" is meritless. Columbia.Br.39. The Board weighed the evidence before it and, in light of Tsien's express teachings, rejected Columbia's argument that skilled artisans would have disregarded these express teachings. A23. The Board found that Illumina met its burden to prove that Tsien disclosed the base-labeled embodiment, finding persuasive the express disclosure of Tsien in view of the expert testimony.

While the Board noted that Columbia failed to explain how Tsien disparaged or taught away from a base-labeled embodiment, this was not impermissible burden shifting, but simply the Board's thorough review of the evidence and weighing of the competing arguments to confirm it should not discount the explicit teachings of Tsien. *Id*.

B. Those Of Skill In The Art Would Have Been Motivated To Use A Deazapurine In Place Of A Purine For DNA Sequencing

Given the prior art and Columbia's cancelation of all claims without a deazapurine requirement, the key issue on appeal is whether it would have been obvious to one skilled in the art to use a deazapurine as an alternative to a purine. Columbia complains that the Board made an "inferential leap" in concluding that one of skill in the art would have found this to be obvious. Columbia.Br.42. This ignores the teachings of Tsien and the state of the art.

As to using deazapurines, Tsien expressly teaches using the nucleotides described in the landmark Prober article. Prober unquestionably discloses only 7-substituted deazapurines. *See supra* at 8, 16-18. Tsien ***broadly*** states that the synthesis scheme for ddNTPs used in Prober should be used in Tsien to produce fluorescent dNTPs: "One quite versatile scheme is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags." As Tsien explains,

Prober's 7-substituted deazapurines with fluorescent labels are successfully incorporated by Tsien's preferred polymerase, Sequenase™:

> One method involves the use of a fluorescent tag attached to the base moiety….This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence….***Prober et al. (1987) show enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™***.

A3029:5-18. Faced with this evidence, Columbia contends that the Board never identified any motivation to use a deazapurine with Tsien. Columbia.Br.43. But this ignores the Board's detailed walk-through of Tsien's multiple references to Prober. *See* A18-19 ("Thus, even if labeling at the C-8 position is superior, Prober I's method is still reasonably suggested by Tsien, which characterizes Prober I as showing 'enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™.'"). Tsien's pointer to Prober is explicit encouragement to use deazapurines because Prober only discloses deaza-type purines.

None of Columbia's responses are meritorious. First, Columbia contends that Tsien refers to Prober only for pyrimidines, not purines. Columbia.Br.43. This is incorrect, and there is very substantial evidence supporting the Board's finding to the contrary on this fact question. A17-20. Tsien ***broadly*** states that the synthesis scheme for ddNTPs in Prober should be used to make dNTPs for SBS. A3030:12-14. Prober does not distinguish between purines and pyrimidines, but instead teaches "a novel set of ***four*** chain-terminating dideoxynucleotides." A3062

col.1. By definition, this includes two pyrimidines and two purines.[7] One skilled in the art would not have taken the general reference in Tsien and applied it narrowly to Prober—a reference that teaches both pyrimidines and purines and that highlights the benefits of the 7-position of a 7-deazapurine for both. And there is certainly substantial evidence supporting this finding even beyond the teachings of the prior art. A3181-3182[Weinstock Decl.] ¶¶ 66-67.

Next, Columbia contends that one of skill in the art would not "abandon" the disclosure in Tsien that the C-8 position of a purine is "ideal" for base-labeling. Columbia.Br.43. Columbia does not, however, contend that Tsien teaches away from the claimed invention. Nor could it make such a contention because Tsien never disparages alternative labeling positions and thus cannot be said to teach away. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) ("A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions."). To the extent Tsien expresses a preference for C-8 labeling, that preference is immaterial given the express teaching in Prober.

Finally, Columbia contends that a skilled artisan would have disregarded a combination of Tsien and Prober because Prober describes ddNTPs for Sanger

[7] Of the four bases that make up DNA, two are purines and two are pyrimidines.

sequencing, not dNTPs for SBS. Columbia.Br.44. According to Columbia, one of skill in the art would not have looked to a description of ddNTPs for Sanger sequencing to "design new ***dNTP*** analogues." *Id.* (emphasis in original). This argument is belied by the evidence. Tsien is an SBS reference, and it undisputedly refers to Prober as disclosing techniques for making ddNTPs that are applicable to the synthesis of dNTPs for SBS. A3030:10-14.

Other prior art SBS references, such as Anazawa, include similar disclosures. *See* A5029[Anazawa] (citing Prober as disclosing a technique for making labeled dGTP). Dr. Trainor acknowledged as much. A3797 ¶ 33. Dower also expressly draws the analogy between ddNTPs used in Sanger sequencing and dNTPs used in SBS, given the similarity of the sequencing reactions in both. A3086[Dower] 14:50-59. Dr. Ju's patent, like Tsien, itself states that the claimed dNTPs could be made using "well-established" procedures taught by Prober and Hobbs that were originally used for ddNTPs. A143(24:64-67).

Even without Tsien's express pointer to Prober, a person skilled in the art would have been motivated to use a deazapurine rather than a purine base. Seela broadly teaches using deazapurine nucleotides "in those sequencing methods for DNA in which the use of DNA polymerase is necessary," which certainly includes SBS. A3157(4:6-7).

Further, as discussed above, by 1999, deazapurines labeled at the 7-position had become the most widely used bases for DNA sequencing with labeled nucleotides in both Sanger sequencing and SBS. *See supra* at 8. By 2000, DNA sequencing was predominantly performed using labeled 7-deazapurines in place of purines. A3598:6-8[Weinstock Dep. Tr.] ("The 7-position was one that was very well known, and much – much of the work was done focusing on the 7-position."). As Illumina's expert explained, the C-7 position of a deazapurine was widely used:

> Because the 7-position, in particular the 7-deaza, as I said before, has been widely used during that time frame…almost 15 years preceding most of this, people were familiar with that, there was wide availability of it, you could buy it from the agent companies…if you want to talk about something that's ideal,…something that has been vetted very broadly in many, many different DNA synthesis applications[,] which is easily available, which people know how to handle…that has a certain ideal nature to it, too. And I think that…certainly one of the reasons why somebody with skill in the art, when they're trying to think about where they would like to attach something to a purine, they would think of the end 7-position.

A3453:1-12.

Columbia's expert likewise confirmed the ubiquity of C7-substituted deazapurines:

> **Q.** Okay. You do see the point that Seela is making here that the 7 position of 7-deazapurines is an ideal position for the functionalization of DNA with reporter groups in this context?
>
> **A.** Well, he's saying you can have anything there and without the reporter. You can put the reporter on later and it didn't

> make a difference, so the linker that–and he showed earlier that simple organic groups that are big work and he's saying, ***Gee, if you what to put a big dye out there you can probably do that***.
>
> **Q.** Right.
>
> **A.** ***But we kind of already knew that, I mean this is '97. We had Prober. We had a slew of Applied Bio-Systems showing the—that the 7 position of deazapurine for the Sanger sequencing at least was just fine. And it didn't need Seela to tell him that that was going to work. It worked***. And, in fact, this is somewhat–this is a little bit redundant, although it's a different field but fair enough.

A4380:7-4381:9. Columbia ignores Dr. Weinstock's opinion that the near ubiquitous adoption of C7-substituted deazapurines—having been much better vetted than any alternative—would have led a skilled artisan to use such deazapurines.

The reason for the popularity of deazapurines was, of course, its well-known benefits. This provided further motivation to use them in SBS. *See supra* at 9-10. Columbia did not dispute that it was known that C7-substituted deazapurines minimize the interference with the incorporation of nucleotides into a DNA strand by a polymerase and result in more stable DNA end products that better allow subsequent incorporations. A5102(27:44-59); A3603:21-3604:1[Weinstock Dep. Tr.]; A4361:8-11, A4408:19-25[Trainor Dep. Tr.]. Additionally, it was known that deazaguanine–based nucleotides allowed for better sequencing guanine-cytosine rich DNA regions and that attachment at the deazapurine 7-position improved

tether attachment. A3378:5-3379:2, A3393:4-3394:12, A3399:24-3403:4[Weinstock Dep. Tr.]; A3176 ¶ 49.

Columbia argues that skilled artisans would have ignored deazapurines for SBS, supposedly because they would have thought deazapurines offered benefits only for the electrophoresis that is specific to Sanger sequencing. Columbia.Br.26. But Dr. Weinstock explained at length why skilled artisans would have understood that deazapurines improved the sequencing of guanine-cytosine rich regions in SBS, not just electrophoretic DNA sequencing. A3393:11-12 ("That's one of the problems of GC-rich regions. But as I said earlier, it's not limited to electrophoretic DNA sequencing methods."); A3177 ¶¶ 54-55; A3378:5-3379:2; A3393:5-3394:9, A3399:24-3403:4[Weinstock Dep. Tr.]. Likewise, it was known that "unnatural 7-deazapurines" could be used to attach a linker without otherwise destabilizing the "glycosidic linkage" between the sugar and base, which would cause the nucleotide to disintegrate. A5093-5094[Hobbs](10:67-11:4); A3176 ¶ 49. SBS, of course, relies upon the base staying connected to the sugar because this is required for proper base-pairing to add subsequent nucleotides.

These well-known benefits would have provided more than enough motivation to use a deazapurine in place of a purine. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1363 (Fed. Cir. 2007) ("one of ordinary skill in the art would have favorably considered [the added salt] because of its known acid strength,

solubility, and other known chemical characteristics as reported in…prior art."). As such, there is substantial evidence confirming the Board's decision to invalidate the claims in view of the combination of not just Tsien and Prober, but the combination of Tsien and Seela.

C. Skilled Artisans Would Have Had A Reasonable Expectation Of Success Making And Using The Claimed Nucleotides For SBS

Columbia contends that one of skill in the art would not have had a reasonable expectation of successfully making and using the claimed nucleotides. The Board did not, as Columbia contends, fail to make findings on this issue. Columbia.Br.28. As shown above, the prior art repeatedly teaches the very techniques that Columbia alleges are novel and unexpected. The Board identified key pieces of such art and explained why it established a reasonable expectation of success, as confirmed by the testimony of Columbia's own expert. A24-25. Substantial evidence thus confirms what commonsense makes clear: If those in the art truly felt the claimed nucleotides could not be made or used, they would not have been so frequently suggested.

1. A Skilled Artisan Would Have Had A Reasonable Expectation of Success in Synthesizing the Claimed Nucleotide

Columbia contends that the "only evidence in the record before the Board indicated that a skilled artisan would not have had a reasonable expectation of

success in making the claimed nucleotide by 'combining' Tsien and Prober." Columbia.Br.47. Columbia relies largely on Dr. Trainor's bald contention that one would have had to "create completely new chemical procedures," which would be "difficult" and that the outcome supposedly could not be "predicted." Columbia.Br.46. Dr. Trainor admitted that, despite leaving the sequencing field long before the date of invention, he did no investigation to verify his blanket assertions about the state of the art.[8] A4319:17-23, A4320:17-24, A4321:24-4322:19. It was not error for the Board to find unpersuasive Dr. Trainor's unverified positions.

During cross-examination Dr. Trainor admitted that every step of the synthetic process would have been understood to be within the level of ordinary skill:

- Using a starting deazaguanine with a 7-iodide for linker attachment. A4251:7-23[Trainor Dep. Tr.] ("I presume that a person skilled in the art would figure out how to do that. It would take some time and this was a 20-step synthesis in our–in our work, so–but that information was available to the person.").

- Attaching a cleavable alkynylamino linker to the 7-iodo position. A4249:13-4250:15 ("Well, certainly in the year 2000 that coupling was well established because every company

[8] In the mid-1990s, Seela's group published procedures for synthesizing the necessary C7-substituted deoxy versions of the deazapurines, which Dr. Trainor declared had not been made before 2000. A5258-5259 (compounds 3,7, and 8); A5272 (compounds 6 and 8c).

that–the companies that were selling dye terminators were all using that coupling reaction….").

- Attaching a fluorescent label to the alkynylamino linker. A4263:23-4264:5 ("**Q.** You said that the reaction would be trivial but that you might have to do a little bit of work but that it would be within the skill of one of ordinary–of ordinary skill in the art. **A.** A-hum."); *see also* A4242:7-4243:5, A4414:19-4415:9.

Moreover, at least with respect to C7-substituted deazaadenine, Dr. Trainor's suggestion that there would not have been an expectation of success contradicts statements he made in his own patent in the relevant time frame. A5102-5103(28:62-29:18); A4315:8-A4316:2.

The '698 patent itself acknowledges that the claimed nucleotides could be made using "well-established" procedures taught by ***both*** the prior art Prober and Hobbs references, which disclosed techniques that were originally used for making ddNTPs. A143(24:64-67). Just as one might substitute cherries for apples in an apple pie recipe to make a cherry pie instead of an apple pie, one of skill in the art would have used the "well-established" procedures of Prober and Hobbs for making labeled ddNTPS by using dNTPs as the starting point instead of ddNTPS. This is confirmed not just in Dr. Ju's patents, but in the prior art as well. Tsien refers to Prober as disclosing techniques for making ddNTPs that are applicable to the synthesis of dNTPs. A3030:12-16 ("One quite versatile scheme is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags.

Structures A, B, C and D below illustrate the type of fluorescent dNTPs that result from these synthetic approaches."). Likewise, Anazawa cites the schemes of Prober as being useful for making labeled dGTP. A5029.

As Dr. Trainor testified, scant direction is included in Dr. Ju's patent regarding how to make the claimed nucleotides beyond its reference to Hobbs:

> **Q.** Is there any reference in the Ju patent to how to synthesize this molecule, other than the sentence that says, "It's prepared using well-established procedures," that's citing to your article and your patent?
>
> **A.** Well, I have to take a look because it wasn't something I was asked to opine on in this–in the declaration.
>
> (Dr. Trainor reviews)
>
> **A.** ***I don't see any – any particular detail that I can refer to at this point.*** Certainly, he seems to be referring to Hobbs. If you go to line–column 27, beginning on line 28.

A4246:17-4248:23. If, as Dr. Trainor contends, new procedures were needed to make the claimed nucleotides, the '698 patent would have included these procedures and would not have simply stated that one should use "well-established" procedures to make the claimed nucleotides. A143(24:66); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir.

2007). These "[a]dmissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness." *Id.*[9]

The "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc.*, 480 F.3d at 1364. The evidence presented at trial shows that there was not even a tiny "degree of unpredictability" as to whether a skilled artisan could successfully make the claimed nucleotides.

2. Incorporation of Nucleotides by Polymerase was Predictable As Established By The Prior Art

Substantial evidence confirms that those of skill in the art would have expected a DNA polymerase to incorporate nucleotides of the type claimed by Dr. Ju. To begin with, base-labeled nucleotides and 3'OH capping groups were both independently shown to work. Numerous prior art references explicitly disclose the successful incorporation of base-labeled nucleotides. *See, e.g.*, A3175 ¶¶ 46-48 (noting that Prober and Hobbs taught that a base-labeled nucleotide could be successfully incorporated by a polymerase and citing additional benefits of base-labeling). Nucleotides with bulky base labels at the 7-deaza position were known

[9] Columbia argues for the first time on appeal (in a footnote) that it is improper hindsight to rely on the patent's admission relating to the conventional nature of the synthesis and its citation to Prober and Hobbs. Columbia.Br.46 n.11. However, Prober is cited in Tsien. A3029:16-18; A3030:10-14. And the evidence shows that Hobbs was understood by skilled artisans as the document describing synthesis of Prober's nucleotides. A3175 ¶ 47.

to be successfully incorporated, a fact cited in Tsien as a benefit of the base-labeled embodiment. A3029:10-12 ("This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence.").

The prior art also showed that 3'-OH blocking groups could be incorporated by a polymerase. *See* A5152[Metzker's *Termination of DNA synthesis*] Table 2; A3666:12-16[Weinstock Dep. Tr.] (describing Metzker's finding that a blocking group can be incorporated without interfering with the DNA polymerase); A3471:19-3473:14 (describing precedent in the art that this would work).

As the Board found, there was no reason to believe that "two structures which are known to work"—a labeled base and 3'-OH cap—"would not work when combined." A25. This finding was supported by substantial evidence, including (1) Dr. Weinstock's testimony, explaining that the C7-deaza and 3' sugar positions of a nucleotide operate independently, A3652:15-23, (2) Tsien's express reason for disclosing this route was because the evidence suggested it would work, A3027:1-12, A3028:36-3029:16, and (3) objective evidence from others working independently of Dr. Ju demonstrating that those in the art were not deterred, as Dr. Trainor suggested. *See supra* at 11-14.

3. The Board Properly Addressed The Level Of Skill In The Art

Columbia complains repeatedly that the Board erred by failing to acknowledge that the level of ordinary skill in the art includes sophistication in synthetic chemistry beyond expertise in sequencing. Columbia.Br.36-37. Columbia's complaint is illogical. This Court has explained that it "is generally easier to establish obviousness under a higher level of ordinary skill in the art." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1366 (Fed. Cir. 2012); *see also Innovention Toys, LLC v. MGA Entm't, Inc.*, 637 F.3d 1314, 1323 (Fed. Cir. 2011) ("A less sophisticated level of skill generally favors a determination of nonobviousness, and thus the patentee, while a higher level of skill favors the reverse.").

Here, Columbia's proposed skill level—"skilled in both chemistry and biology"—is ***higher*** than Illumina's proposed skill level—biology and related fields. Columbia.Br.34. If the claims would have been obvious under Illumina's proposed definition, they certainly would have been obvious to one with added skill in the area of synthetic chemistry that Columbia considers important. This is confirmed by the additional evidence—including Dr. Trainor's admissions—showing a reasonable expectation of success. *See supra* at 38-43. There were no material errors in the Board's identification of the skilled artisan. *Okajima v.*

Bourdeau, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the absence of specific findings on the level of skill in the art does not give rise to reversible error 'where the prior art itself reflects an appropriate level and a need for testimony is not shown.'").

In fact, the Board's decision was properly rooted in context-specific competencies of one skilled in the art that it found from record evidence and that are directly relevant to the issues at hand. *See In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (finding no clear error where the Board assessed the level of skill in the art "by appeal to the references of record"). For instance, based on numerous disclosures in the art, the Board recognized that one skilled in the art would have recognized the usefulness of base-labeled nucleotides. A6. Likewise, based on Tsien, the Board discerned that those of skill in the art recognized the value of cleavable tethers for releasing labels attached to base moieties. A15. As another example, based on the testimony of Dr. Trainor and the disclosure of Tsien, the Board determined that one of skill in the art would have recognized the usefulness of deazapurines. A19-20. While the Board did not provide a detached resumé-style definition of the level of skill in the art with generic educational credentials and years of employment, Columbia's contention that the Board "failed to identify" the level of skill in the art is inaccurate.

Columbia's level of skill argument appears to be an attempt to recast a run-of-the-mill expert attack as a missing "skill-level" finding amounting to reversible

error. Columbia contends that Dr. Weinstock did not have enough skill in chemistry to recognize alleged complexities associated with synthesizing the claimed nucleotides. According to Columbia, the Board should have disregarded Dr. Weinstock's testimony and instead adopted Dr. Trainor's opinions. Columbia.Br.40.

Columbia, however, never moved to disqualify Dr. Weinstock. To the contrary, Columbia repeatedly relied upon Dr. Weinstock's testimony. A2173[Substitute Response] ("[Dr. Weinstock's] deposition testimony…confirms many important facts relied upon and positions advanced by Columbia…"). And, as demonstrated throughout this brief, Dr. Weinstock's opinions and the Board's findings regarding the level of skill in the art were amply supported.

In sum, the more educated a person skilled in the art is in synthetic chemistry, the more obvious the claimed inventions. Columbia's insistence that a person skilled in the art would have synthetic chemistry expertise reinforces the Board's decision, it does not overcome it.

D. Solexa's Independent Invention Is Substantial Objective Evidence Supporting The Board's Obviousness Determination

"Independently made, simultaneous inventions, made within a comparatively short space of time, are persuasive evidence that the claimed apparatus was the product only of ordinary mechanical or engineering skill." *Geo.*

M. Martin Co. v. Alliance Mach. Sys. Int'l LLC, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (internal quotation marks omitted). As documented above, the prior art shows that multiple research groups independently arrived at Dr. Ju's claimed nucleotides either simultaneously or before Dr. Ju. *See supra* at 11-14. Solexa conceived of an SBS approach as early as December 2001, before any of Dr. Ju's patent applications were published. That approach used nucleotides containing all the allegedly novel features of Dr. Ju's patent claims. A3746[Solexa Patent App.]. Likewise, in June 2000—which is before Dr. Ju's earliest claimed invention date—Odedra and colleagues at Amersham also independently conceived of an SBS technique using nucleotides with the allegedly novel features.

The reason these groups independently arrived at the nucleotides now claimed by Dr. Ju is that they were obvious in view of the numerous prior art references that disclosed the same combinations along with the well-established rationale for making them.

E. The Board Properly Held That Claims 5, 11, And 12 Are Obvious

Claims 5 and 11 add the use of a "plurality of DNA templates immobilized on a solid surface." Dependent claim 12 further limits claim 11 to using a "microarray." The Board held that claim 11 was obvious in view of the

combination of Tsien and Prober,[10] and that claims 5 and 12 were obvious in view of the combination of Tsien, Prober, and Rabani.

As an initial matter, Columbia waived its arguments for claims 11 and 12 because it did not argue non-obviousness of claims 11 or 12 in the IPR. 37 C.F.R. § 42.120. Even on appeal, for claim 11, Columbia only argues the "different" language of amended claim 25. A4200:4-06:10, A4683:22-84:15. For claim 12, while Dr. Trainor made statements about microarrays, Columbia did not argue that this limitation was non-obvious in its patent owner's response, or otherwise, in the IPR, thus waiving it. 37 C.F.R. §§ 42.6(3), § 42.23.

Regardless, substantial evidence presented at trial supports the Board's decision. Tsien disclosed a DNA microarray. A3511:2-A3512:2. Additionally, Rabani applies to SBS and discloses the detection of "multiple probes (*i.e.* in arrays with parallel detection provided)." A3107:12-13. Dr. Trainor conceded that Rabani discloses an SBS microarray in connection with a massively parallel sequencing scheme. A4452:8-4453:22[Trainor Dep. Tr.] ("[T]hat would be a microarray of templates, yeah. I would think so."). He further confirmed that at

[10] Columbia contends that the Board did not address the "plurality of nucleic acids" limitation in claim 11. Columbia.Br.28-29. However, this limitation also appears in claim 5, for which the Board adopted the findings from its decision to institute, which includes citation to evidence in Rabani satisfying this claim element. A27-28, A90.

the time of Dr. Ju's patents, microarrays were "common in the field." A4454:3-7. As Dr. Weinstock explained, it would have been obvious to one skilled in the art to "modify[] the sequencing process taught by Tsien (including the 7-deazapurine features of Prober I) to…use an array format as taught by Rabani." A3187[Weinstock Decl.] ¶ 77; *see also* A3178-79 (Dr. Weinstock explains additional motivations to use an array); A3691:4-A3693:21 (Dr. Weinstock's testimony regarding the known advantages of arrays); A3694:21-A3697:12 (same).

In addition, the '698 patent itself acknowledges that "chip format" sequencing, in which a surface with a large number of different attached polynucleotides is used to increase the volume of sequence information, was known and had been widely investigated. As the '698 patent states: "Such a scheme coupled with the chip format and laser-induced fluorescent detection has the potential to markedly increase the throughput of DNA sequencing projects. Consequently, ***several groups*** have investigated such a system with an aim to construct an ultra high-throughput DNA sequencing procedure (Cheeseman 1994, Metzker et al. 1994)." A132(2:11-17); *see also* A3690:4-3691:2 (Illumina's expert confirms that the '698 patent's "chip format" is a description of an array); A3182 ¶ 68 (Illumina's expert explains "chip format" sequencing and confirms that is was well known); A3178-79.

III. Columbia's Secondary Considerations Arguments Do Not Negate The Substantial Evidence Supporting The Board's Obviousness Determination

Columbia contends that the Board "wrongly disregarded" evidence of secondary considerations. Columbia.Br.52-53. Not true. The Board's focused consideration of Columbia's secondary considerations arguments was manifest at oral argument and in its written decision. A5188 ("[W]e would like a substantial amount of time to hear about the secondary consideration."). Almost 20 pages of the oral argument transcript and 11-pages of the Board's final written decision are directed to Columbia's secondary considerations arguments.

The Board's analysis was grounded in well-settled law that there must be a nexus between the patented invention and evidence of secondary considerations. As to nexus, the most important aspect of Columbia's arguments is what it does ***not*** say. Specifically, Columbia never contends that using a deazapurine is connected to any secondary consideration of nonobviousness. Deazapurines were the dominant type of purine used in sequencing by the time of Dr. Ju's patent application, and their use is the only colorable difference between Tsien and the claims of the '698 patent. *See supra* at 1-4, 9-10. By failing to point to any objective evidence establishing that using a deazapurine was not obvious, Columbia effectively concedes that it was convention—not a stroke of invention—that led to the claimed method.

Indeed, for each claim and for each secondary consideration, Columbia alleges a nexus based solely on a concept taught in the prior art: the separation of the cleavable chemical group at the 3′-OH position of the sugar from the detectable label by instead attaching the label to the base. All of Columbia's briefs in the three companion cases present this exact same argument and evidence regarding secondary considerations without differentiating among patents or the specific features of individual claims. Columbia's total failure to tie specific features of the different claims in three different patents to secondary indicia reinforces that there is no meaningful nexus to anything other than the prior art.

"To be afforded substantial weight, the objective indicia of non-obviousness must be tied to the ***novel*** elements of the claim at issue." *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013); *see also In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Where the offered secondary consideration actually results from something other than what is ***both claimed and novel*** in the claim, there is no nexus to the merits of the claimed invention.").

Given the strength of the art, the presence of secondary considerations of obviousness in the form of simultaneous invention and Columbia's inability to establish a nexus, Columbia's secondary considerations argument does not raise a legitimate question about the correctness of the Board's obviousness

determination. *See Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (holding that secondary considerations did not overcome the "strong case of obviousness" where the asserted features were a well-known alternative in the prior art); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1354 (Fed. Cir. 2012) (the Federal Circuit has "rarely held that objective evidence is sufficient to overcome a prima facie case of obviousness" because "[f]ew cases present such extensive objective evidence of nonobviousness").

A. Columbia's Alleged Unexpected Properties Are Not Connected To The Claimed Invention

Unexpected results "must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed.Cir.2006). Columbia's sole complaint about the Board's treatment of unexpected properties is that the Board erroneously used Tsien as a baseline because Tsien allegedly discloses only a "hypothesized and uncommercialized method." Columbia.Br.63. According to Columbia, the Board should have used pyrosequencing as a baseline because it was "the only commercial embodiment of SBS at the time of Dr. Ju's invention." *Id.*

Columbia's position is without merit. First, Columbia cites no authority that disqualifies uncommercialized prior art systems from being the closest prior art.

To the contrary, the law is clear that uncommercialized prior art systems can be the closest prior art. *In Re Baxter Travenol Labs,* 952 F.2d 388, 391-92 (Fed. Cir. 1991) (using an experimental system not approved by the FDA as the closest prior art). Columbia's proposed commercialization requirement is particularly inapposite in this case. Dr. Ju's own patent was theoretical, did not provide data, and was not reduced to practice ***until six years later*** using important changes not disclosed in the patents at issue. *See* A3470:13-3471:5; A5417:9-16, A5604:18-5605:4; A4130:15-19, A4131:14-4133:24; A3992-94.

Second, Columbia cites no evidence that pyrosequencing is closer prior art than Tsien, which, unlike pyrosequencing, discloses SBS using a nucleotide with a labeled base and a removable group on the 3'OH. Although Columbia's expert asserted that pyrosequencing was the closest prior art, he provided no explanation. *See* A3871-3876 ¶¶ 200-14.

Further, "for the unexpected results…to have substantial weight, there must be a nexus to some aspect of the claim ***not already in the prior art***." *In re Huai-Hung Kao*, 639 F.3d at 1069. Columbia's expert testified that the alleged unexpected success of Dr. Ju's patent was "***made possible*** by the fact that Dr. Ju's nucleotide analogues separated the cleavable chemical group at the 3′-OH position of the sugar from the detectable label, which was placed instead on the base." A3873 ¶ 207; A3871-72 ¶ 202 (mentioning only base-labeling and a cleavable

linker and not a deazapurine). Thus, Dr. Trainor opined that the alleged unexpected success of Dr. Ju's patent was "made possible" by the very feature previously taught in Tsien, Dower, and Stemple.

B. Columbia Never Established A Nexus Between The Claimed Invention And Illumina's Commercial Success

Just as with unexpected properties, if "commercial success is due to an element in the prior art, no nexus exists." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011). Yet, the very features proclaimed by Columbia to be the reason for Illumina's commercial success (attachment of the label to the base via a cleavable linker) were already known in Tsien, Dower, and Stemple. Although the claimed invention further requires a deaza-substituted base, Columbia never once contended that this contributed to Illumina's commercial success. In 27 paragraphs addressing commercial success, Dr. Trainor never mentions deazapurine at all. The substantial evidence before the Board did not show that the nexus between Illumina's success and the patented invention was anything other than what was described in Tsien, Dower, and Stemple. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010), vacated by *Therasense, Inc. v. Becton, Dickinson & Co.*, 374 F. App'x 35 (Fed. Cir. 2010), reinstated in relevant part by *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1296 (Fed. Cir. 2011) (affirming district

court's rejection of patentee's secondary considerations where the patentee's primary witness conceded that commercial success was due to features in the prior art).

In addition, while Columbia points to Illumina's sales dating back to 2006, Columbia's expert testified that he did not know if earlier products embodied features of the claims. A4111:11-A4116:17. Dr. Trainor did not even know if Illumina would have been just as successful using a different sequencing method. A4495:2-A4497:12.

If anything, the substantial evidence showed that Illumina's commercial success was "due to extraneous factors other than the patented invention, such as advertising, superior workmanship, etc." *Demaco Corp. v. F. Von Lansdorff Licensing*, 851 F.2d 1387, 1393 (Fed. Cir. 1988). Columbia's expert had no knowledge (and did not seek out knowledge) of what influenced purchasing of next generation sequencing (including Illumina's) products. *See* A4068:13-A4069:20, A4494:13-A4497:12. By comparison, Dr. Weinstock had run two major genome centers, purchasing numerous sequencing instruments. A3162-3163 ¶¶ 9-10. He testified to a list of factors unrelated to the claimed nucleotides that do, in fact, lead to success in commercial sequencing. These included: (1) the cost of instruments and reagents, A3582:6-8; (2) ease of sample preparation, A3582:8-11; (3) automation and ease of use, A3582:12-18; (4) ease of data analysis after

sequencing, A3582:19-22; and, (5) the quality of customer service, A3582:23-3583:12. Consistent with this, according to Columbia's own expert, [redacted]

On appeal, Columbia argues for the first time that the claimed features are not "readily available" in Tsien because it was not a "***commercial embodiment***," and/or because "***each element was separately disclosed*** in various embodiments" of Tsien. Columbia.Br.61. None of the cases cited by Columbia suggests that claimed features are "readily available" only if they are part of a commercial product. In all the cases cited by Columbia, no nexus was found. Columbia's proposed "commercial embodiment" rule is untenable under this Court's law, which is not limited to what was "readily available" in the prior art, but extends to anything "disclosed," "known" or "due to an element" of the prior art. *See, e.g.*, *Asyst Technologies*, 544 F.3d at 1316 ("[F]ailure to link that commercial success to the features of its invention that were not disclosed in [the prior art] undermines the probative force of the evidence pertaining to the" commercial success); *Ormco Corp.*, 463 F.3d at 1312 (Fed. Cir. 2006) ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."); *Tokai Corp.*, 632 F.3d at 1369 ("due to an element").

C. There Was No Copying Of Dr. Ju's Patents

Like Columbia's other evidence of secondary considerations, its copying allegations are immaterial because they are not tied to the "novel elements of the claim at issue." *Institut Pasteur*, 738 F.3d at 1347; *cf. Transocean Offshore*, 699 F.3d at 1352 (finding substantial evidence to support indicia of obviousness where an internal document expressly tied copying to the "features of Transocean's invention, which it distinguishe[d] from the [features] taught in the prior art.").

[redacted] The only documents upon which Dr. Trainor based his conclusion were [redacted] Again, this is not a novel feature, but an element disclosed in Tsien, Dower, and Stemple. Regardless, there is no evidence that Manteia copied a claimed product—neither presentation discloses a deazapurine, which, as explained in this brief, is the primary feature relied upon by Columbia as inventive relative to Tsien.

Additionally, Dr. Trainor did not investigate or consider whether Illumina or Solexa independently developed the technology before Manteia's 2002 presentation. A4073:15-4076:4. The evidence before the Board conclusively

demonstrated that the allegedly-copied technology was independently invented by Solexa no later than December of 2001—prior to the earliest publication date of Dr. Ju's patent—precluding any possibility of copying based on Solexa's 2004 acquisition of Manteia. *See supra* at 11-14.

Nevertheless, Columbia complains that the Board erred by not separately addressing Columbia's copying allegations. The Board, however, expressly recognized that Columbia asserted copying as a secondary consideration and, after listing ***all*** of Columbia's secondary considerations, stated that it had "considered this evidence." A29. *See In re Dixie Restaurants, Inc.*, 105 F.3d 1405, 1407 (Fed. Cir. 1997) (noting that the Board's decision stated "we have considered each applicable factor" and finding "no error in the board's decision to focus on the [relevant] factors it deemed dispositive.").

Even if the Board did not consider copying, such an error is harmless. *See Ecolochem*, *Inc.*, 227 F.3d at 1380 (district court's error with regard to copying did not carry great weight "in light of all the secondary considerations, combined with the other evidence and findings on the prior art"). Columbia's already scarce evidence of copying is diminished because, as noted above, both Solexa and Odedra independently developed the claimed nucleotide analogue. *See Vandenberg v. Dairly Equip. Co.*, 740 F.2d 1560, 1567-68 (Fed. Cir. 1984) (finding evidence of copying was not a "decisive factor" because, in part, "[t]he

basic concept of the invention occurred independently" to the challenger). Further, "a showing of copying is ***only equivocal evidence*** of non-obviousness in the absence of more compelling objective indicia of other secondary considerations." *Ecolochem, Inc. v. S. California Edison Co.*, 227 F.3d 1361, 1380 (Fed. Cir. 2000). As shown herein, Columbia does not have compelling evidence of any secondary consideration.

D. The Discussions Between Illumina And Columbia Do Not Show "Respect" For Dr. Ju's Alleged Invention

The secondary consideration Columbia emphasizes the most is based on the alleged licensing discussions between Columbia and Illumina. This Court has held, however, that "only little weight can be attributed to" licensing evidence "if the patentee does not demonstrate a nexus between the merits of the invention and the licenses of record." *In re GPAC*, 57 F.3d at 1580 (internal quotation marks omitted). Although Columbia presented evidence of discussions between Illumina and Columbia, none of it is connected to the patented invention and there is no consummated license.

Columbia submitted no testimony from anyone involved in the alleged licensing discussions. Instead, Columbia relied on a handful of email communications, most of which pre-date the August 2007 filing of the patent application that ultimately led to the asserted claims. In this pre-2007 time frame,

Illumina was exploring options for expanding into the sequencing business and was assessing potential collaborative partners. Thus, the email correspondence relied upon by Columbia reflects Illumina's high-level interest in sequencing generally and is not exclusive to a particular aspect of DNA sequencing. *See, e.g.*, [redacted] A3995.

None of the email relied upon by Columbia mentions either the '698 patent or the patents involved in the two companion cases—and nothing about the specific features which supposedly make the claims patentable. Any such discussions prior to 2007 could not possibly have been directed to the patents asserted now because the earliest any such patents were filed was June 2007; the claims predating the 2007 filing were narrower in scope.

To the extent Illumina's pre-2007 discussions with Columbia referred to specific intellectual property, this property was set forth in a list of 18 patents and three patent applications, as well as seven invention reports, none of which are the patents at issue now.[11] *See* A4010. What this list shows is that there was a broad

[11] The Board stated that "Illumina did not challenge Columbia's description of its attempt to license the technology in their response to Columbia's § 42.120 filing."

discussion of an entire SBS patent portfolio; nothing is tied to the merits of the alleged inventions involved here. In these circumstances Columbia cannot establish a nexus. *In re GPAC*, 57 F.3d at 1580 ("Because, in affidavits reciting the licensing history of the '111 patent, GPAC did not establish which claim(s) of the patent the licensing program incorporates, GPAC has not shown that licensing…arose out of recognition and acceptance of the subject matter claimed in the '111 patent.").

While Illumina discussed a potential partnership with Columbia, it was concurrently considering numerous other candidates, including Solexa, who had demonstrated "clear sequencing" long before Dr. Ju at Columbia.

> There was the opinion from people I trust that Jingyue is ahead in development of reversible terminators. ***However, Solexa showed real progress and clear sequencing of about 30 bases with fully implemented four-color reagents.*** They sequenced and assembled a BAC from 15X coverage with 99.997% accuracy, and also several long-range PCR products.

A3996. [redacted]

Although after 2007 there were subsequent discussions among Dr. Ju, Columbia, IBS (Columbia's licensee to Dr. Ju's SBS technology), and Illumina,

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A38. In fact, Illumina presented such arguments during the hearing. A5233-5235[Oral Arg. Tr.].

the record shows that these were arms-length negotiations initiated primarily by Dr. Ju and IBS—not Illumina. For instance, in a 2010 email to Jay Flatley at Illumina, Dr. Ju cited Illumina's "spectacular progress" and "great leadership and vision," and expressed his interest in collaborating with Illumina.

> Warmest congratulations for the spectacular progress that Illumina is making under your great leadership and vision. As you know, our main research supported by NIH at Columbia is on conceiving new ideas and developing novel approaches for DNA sequencing. It would be great to figure out a way to put together the synergy of the global industrial leader (Illumina) and a world-class University (Columbia), which will keep lead the field in both the market and top research.

A4028[Email]. While Illumina and Columbia continued to consider the possibility of collaborating, mostly at Columbia and their licensee's (IBS) prompting, nothing materialized and Illumina never licensed any intellectual property from Columbia. *See, e.g.*, A4014[Email]; A4015[Email]; [redacted] Columbia cites no authority for the counterintuitive proposition that such evidence of preliminary and/or unconsummated business discussions is an indicator of non-obviousness.

Columbia effectively concedes that its evidence of licensing is not based on novel aspects of the claims. According to Columbia, a "key technological component[]" that Illumina allegedly wanted to license was "reversible terminators with a cleavable dye." Columbia.Br.13,56. This is precisely what is disclosed in

Tsien, Dower, and Stemple. Because the evidence of licensing "actually results from something other than what is both claimed and novel in the claim, there is no nexus." *In re Kao*, 639 F.3d, 1068.

IV. The Board Did Not Commit Any Structural Or Procedural Errors

Columbia alleges that the Board failed to honor the adjudicative nature of IPR, and instead treated the process as a renewed patent examination in which it relied upon its own expertise rather than record evidence and erroneously placed the burden upon Columbia to prove patentability. Columbia.Br.32-34. Columbia is wrong.

The Board's final written decision confirms that the Board operated under the mandated oppositional model for IPRs. Indeed, it includes a thorough recitation of ***both*** sides' positions and a weighing of the evidence, including a detailed discussion of the parties' expert witness testimony. A16-27. If the Board were simply relying on its own uniformed reading of the prior art, as Columbia alleges, this detailed analysis would be absent.

Columbia cherry picks sections of the decision in which the Board quotes from the art itself as proof that the Board's review was somehow insulated from the expert testimony. Columbia.Br.41. It is not impermissible for judges in an adjudicatory process to read, evaluate, and quote prior art in the context of the overall record. This Court properly does so all the time.

In any event, Columbia ignores the full scope of the Board's analysis. For instance, Columbia complains that the Board relied upon its own creative interpretation of Tsien to find that it discloses a cleavable linker attached to the base. *Id*. In fact, the Board relied upon Dr. Trainor's admission that Tsien suggests precisely this. A21. Likewise, in another portion of the Board's decision cited by Columbia as an example of the Board relying upon its own expertise, the Board actually relied on Dr. Trainor's testimony, which contradicted his declaration. *See, e.g.*, A19 ("Dr. Trainor, himself, admitted that fluorescently labeled deazapurines had been used in the prior art.") (citation omitted).

As set forth in *Graham*, the Board describes the scope and content of the prior art, including a pin-citation on nearly every page of its decision to specific disclosures in the art. The Board quotes the prior art no less than 28 times, documenting the black-and-white disclosures rendering Columbia's claims invalid. While "it is impermissible for the Board to base its factual findings on its expertise, rather than on evidence in the record," the "Board's expertise appropriately plays a role in interpreting record evidence." *Brand v. Miller*, 487 F.3d 862, 869 (Fed. Cir. 2007). The Board's scrupulous adherence to the evidence confirms that it did not act as an independent expert, but simply engaged in its adjudicatory interpretive role.

Further, the Board did not impermissibly rely on facts "found" in its decision to institute. Columbia.Br.34. Columbia cites only the Board's decision that claims 5 and 12 are rendered obvious by the combination of Tsien, Prober, and Rabani. As the Board noted, Columbia did not identify any defect in the Board's findings or reasoning that led to institution in its patent owner's response. A2191-92. Faced with no new evidence or argument it found to be compelling, the Board cited the relevant portions of its decision instituting IPR and adopted those in its final written decision. A27-28. Columbia cites no authority establishing that it was reversible error for the Board to decline to regurgitate its prior careful analysis in even greater detail.

Finally, the Board did not allow Illumina to dodge its evidentiary burden: a preponderance of the evidence. 35 U.S.C. § 316(e). "Preponderance of the evidence means the greater weight of evidence, evidence which is more convincing than the evidence which is offered in opposition to it." *United States v. C.H. Robinson Co.*, 760 F.3d 1376, 1383 (Fed. Cir. 2014) (internal quotation marks omitted). The Board outlined the evidence before it and fully addressed Columbia's arguments to determine whether Illumina's evidence was "more convincing than the evidence…offered in opposition to it." *Id.* In each instance, the Board explained Illumina's evidence that it found convincing and then turned to evidence offered by Columbia to explain why, for reasons documented herein, it

determined that Columbia's evidence was not convincing. Under Columbia's argument, a Board decision could never review and reject opposition arguments without being accused of shifting the evidentiary burden.

V. There Is No Basis To Reverse The Board's Decision

Columbia seeks reversal of the Board's decision. Such relief is improper in all events.

Columbia moved to exclude certain rebuttal exhibits introduced by Illumina, including sections of the declaration of Dr. Kevin Burgess and numerous references discrediting Dr. Trainor's assertions. A2288. The Board determined that the claims were unpatentable without relying on Illumina's rebuttal testimony and exhibits. A44-45. Therefore, it dismissed Columbia's motion as moot. *Id.*

As documented above, the Board's invalidity conclusion is supported by substantial evidence and should be affirmed. Nevertheless, the rebuttal evidence presented by Illumina constitutes yet additional proof of obviousness, including evidence that contradicts Dr. Trainor's assertions on at least the following points:

- The ubiquity and benefits of deazapurines. A5749[Ex. 1041]; A5734(7:54-65)[Ex. 1032]; A5771-72, A5774-5778, A5815[Ex. 1053] ¶¶ 48-49, 53-56, 144.
- The well-known incompatibility of 3'-OH labeled nucleotides with polymerases. A5722[Welch]; A5802[Ex. 1053] ¶ 107.
- The simultaneous and independent development of Dr. Ju's alleged invention by others. A5128:20-21, A5129:28-30,

A5145[Amersham Patent App. No. 0013276.1]; A5800-5806[Ex. 1053] ¶¶ 101-17

- The ease with which skilled artisans could synthesize Dr. Ju's claimed nucleotides. A5735(10:49-50)[Ex. 1032]; A5258-5259[Ex. 1042]; A5777-5778, A5780-5781, A5785-5799, A5777-78[Ex. 1053] ¶¶ 55-56, A5780-81 ¶¶ 60-61, A5785-98 ¶¶ 70-96, A5799 ¶ 99, A5814 ¶ 140.

Because this additional evidence was not considered by the Board, there is no basis for Columbia's request for this Court to outright reverse the Board.

CONCLUSION

The Board's decision should be affirmed.

Dated: December 29, 2014

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B). This brief contains 13,997 words as calculated by the "Word Count" feature of Microsoft Word 2007, the word processing program used to create it.

The undersigned further certifies that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in Times New Roman 14 point font.

Dated: December 29, 2014

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In accordance with Fed. R. App. P. 25 and Fed. Cir. R. 25, I certify that on this day December 29, 2014, I served the foregoing via the Court's CM/ECF system and electronic mail on the principal attorneys for each party.

Dated: December 29, 2014

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